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Nutritional treatment with branched-chain amino acids in advanced liver cirrhosis

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Abstract: During the last 20 years there has been much interest in nutritional treatment for patients with advanced cirrhosis. Most studies have measured the potential benefit of nutritional supplements of dietary proteins, generic protein hydrolysates, or specific branched-chain amino acid (BCAA)-enriched formulas in regard to nutritional parameters and hepatic encephalopathy. The issue is not definitively settled; data are conflicting and meta-analyses have failed to produce unequivocal results. A consensus review, recently produced under the auspices of the European Society for Parenteral and Enteral Nutrition, concluded that: (1) patients with cirrhosis tend to be hypermetabolic, and a higher-than-normal supply of dietary proteins is needed to achieve nitrogen balance; (2) most patients tolerate a normal or even increased dietary protein intake, without risk of hepatic encephalopathy; (3) a modified eating pattern, based on several meals and a late evening snack, is useful; (4) in severely malnourished patients, amino acid supplements may be considered to provide the necessary amount of proteins to meet protein requirements; (5) in a few patients intolerant to the required protein intake, BCAA supplements may be considered to provide the necessary nitrogen intake without detrimental effects on the mental state, perhaps even improving it. Future studies are needed to quantify the advantage of nutritional support with amino acids or BCAA supplements on overall well-being, complications, and ultimately survival with a long-lasting disease where self-perceived health-related quality of life is a major outcome.

Key words: energy metabolism, liver diseases, nutrition

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Introduction

Since the pioneering study of Fischer and Baldessarini, who firstly linked hepatic encephalopathy to plasma amino acid imbalance via false neurotransmitter synthesis,[1] the area of amino acid therapy in liver disease has attracted attention. Several experimental studies have been carried out to confirm a specific effect of branched-chain amino acids (BCAAs) on protein and amino acid metabolism in the liver, peripheral tissues, and eventually the brain. In addition, in several controlled and uncontrolled clinical studies, BCAAs were given intravenously or orally to patients with advanced cirrhosis, hepatic encephalopathy, or both. After nearly 30 years of debate, the issue is still not settled. Many data have been accumulated, but a specific advantage of BCAA-enriched solutions in hepatic encephalopathy and nutrition in malnourished patients with cirrhosis is far from proved. This review focuses on areas where final answers are still lacking, and where additional data are needed to settle an age-old question.

Hepatic encephalopathy

There is a sound rationale for the use of BCAAs in hepatic encephalopathy, particularly based on the following points.

1. BCAAs may provide an energy source to prevent endogenous catabolism, which contributes to plasma amino acid imbalance. This is mainly the case of cirrhotic patients, in whom BCAAs may be used preferentially as an energy substrate.[2]
2. Exogenous BCAAs may provide the bulk of competition across the blood–brain barrier, preventing entry of toxic amines.[3]
3. BCAAs may directly increase ammonia metabolism in skeletal muscle tissue, sparing ammonia detoxi-

fication in the brain, which is likely to enhance the entry of toxic amines.

On these bases, several attempts have been made to treat patients with cirrhosis and hepatic encephalopathy with pure BCAAs or BCAA-enriched formulas. The expected results differ in relation to the type of encephalopathy. In acute cases, where precipitating factors are of major importance and may determine the final outcome independent of encephalopathy, intravenous BCAAs are supposed to exert a rapid pharmacological action at the blood–brain barrier level. In chronic cases, where acute events are of minor importance, the putative action of BCAAs should be mainly on nutrition, with secondary effects on encephalopathy. Long-term treatment is required.

Intravenous BCAA treatment for acute encephalopathy

Seven randomized controlled clinical trials were reported on intravenous treatment of acute encephalopathy with BCAAs in patients with cirrhosis.[4–10] Despite differences in patient selection, duration of treatment, amount of supplied BCAAs, and type of control therapy, a meta-analysis is possible. In summary, 380 patients were randomized to receive either intravenous BCAA-enriched solutions (201 cases) or isocaloric parenteral nutrition with or without standard treatment (179 cases). In a meta-analysis, Naylor et al.[11] concluded that there was heterogeneity among trials in times of case-fatality rates, a few studies suggesting that BCAAs reduce death rates and others that the treatment group fared worse. When simply pooling the data of these seven studies, the relative risk of death is seen not to be reduced by BCAAs when dropouts are included in the analysis [odds ratio (OR) 0.81, 95% confidence interval (CI) 0.51–1.29; $P = 0.190$].

These results are not surprising. Most patients were treated during acute events, such as gastrointestinal hemorrhage and sepsis. The death rate is high among these patients and is more closely related to precipitating factors than to coma. This also explains the large heterogeneity among studies, probably due to the different selection of patients.

As to recovery rates, no heterogeneity was demonstrable among the five major trials; and BCAAs were found to produce significantly better results than standard treatment.[11] Even after inclusion of the last two negative trials,[9,10] a mildly favorable effect of BCAAs on recovery rates was maintained (OR 1.48, 95% CI 0.96–2.29; $P = 0.037$), and negative trials found either a shorter time to recovery in patients treated with BCAAs[9] or a final outcome better than that observed in the control arm.[10] In summary, the advantage of BCAAs over control therapy remains low in terms of recovery rates from coma in cirrhotic patients with acute encephalopathy, without any effect on survival.

Oral BCAA treatment for chronic encephalopathy

Numerous controlled and uncontrolled clinical trials[12–28] and excellent reviews have been reported on BCAA treatment for chronic hepatic encephalopathy (Table 1). After excluding the uncontrolled studies,[12,23] studies performed in selected groups of patients,[27,28] a purely metabolic study,[24] a study randomized against lactulose, a drug of proved efficacy,[17] and trials in patients with subclinical encephalopathy[14,21,26] where current indices of mental state cannot be used, eight comparable studies remained.[1–15,16,18,20,22,25] These articles were critically revised in the hope of producing a meta-analysis, and several conclusions can be stated.[29]

1. Patient selection is rarely thoroughly described in the studies. In particular, there is mention of the rejected patients only in two studies.[18,30]
2. Duration of treatment is extremely variable (from 3 days to 60 months), which implies different therapeutic hypotheses. Short-term studies assume a direct pharmacological effect of BCAA; long-term studies imply that changes in mental state are mediated by nutritional improvement.
3. Sample size is small in most studies, implying a high risk of type II error.
4. Withdrawal rate is high but is rarely considered.[18,25]
5. The proportion of patients with alcoholic liver disease, who may have chronic alcohol-induced damage to the brain, varies from 29% to 90%.
6. The proportion of shunted patients is between 0 and 100%.
7. The proportion of patients on lactulose similarly varies (from 8% to 100%).
8. The quality score of studies is between 0.199 (poor study) and 0.844 (well-conducted study).

Control therapy was usually casein or dietary proteins; in only a few studies were carbohydrates administered. A total of 131 patients underwent treatment; 104 were treated in a parallel group design and 27 in a crossover design. The two largest studies,[18,25] accounting for 87 patients, were both positive. These studies have a completely different trial design. One was prophylactic, proving that BCAAs are less likely to produce encephalopathy than dietary proteins in subjects with impending coma. The other was therapeutic, showing superiority of BCAAs over casein in patients with encephalopathy on a normal protein diet.

Unfortunately, it was not possible to subject these studies to a meta-analysis with the usual techniques, and individual data were no longer available by the leading authors.[30] Therefore no final conclusion was possible.

Table 1. Controlled trials on oral BCAA treatment for advanced liver disease

Study	Study type	No. of cases	Study period	Alternative treatment	Outcome	Results
Schäfer[12]	nr	8	4–8 weeks	Casein/CHO	Encephalopathy	Dubious
Eriksson[13]	co	7	2 weeks	CHO	Encephalopathy	Not different
Sieg[14]	co	14	3 months	CHO	Psychometry	Not different
Simko[15]	pg	10	3 months	NS	Encephalopathy	Not different
McGhee[16]	co	4	11 days	Casein	Encephalopathy	Not different
					N balance	Not different
Riggio[17]	pg	28	90 days	Lactulose	Encephalopathy	Not different
Horst[18]	pg	26	3 weeks	Proteins	Encephalopathy	BCAA better
					N balance	Not different
Guarnieri[19]	pg	7	3–4 months	CHO/lipid	Encephalopathy	Not different
					N balance	BCAA better
Christie[20]	co	6	3 days	Casein	Encephalopathy	Not different
					Anthropometry	Not different
					N balance	Not different
Egberts[21]	co	22	1 week	Casein	Psychometry	Dubious
					N balance	BCAA better
Fiaccadori[22]	co	10	4 weeks	Casein	Encephalopathy	Not different
					N balance	Not different
Yoshida[23]	nr	40	7–62 months	NS	Survival	BCAA better
Swart[24]	co	8	5 days	Proteins	Psychometry	Not different
					N balance	Not different
Marchesini[25]	pg	61	3 months	Casein	Encephalopathy	BCAA better
					N balance	BCAA better
Plauth[26]	co	23	8 weeks	Placebo	Psychometry	BCAA better
Chin[27a]	co	10	8 weeks	Standard	Anthropometry	BCAA better
San-In Group[28b]	pg	132	1 year	NS	Encephalopathy	BCAA better
					Nutrition	BCAA better

nr, not randomized; co, crossover; pg, parallel group; NS, not specified; BCAA, branched-chain amino acids; CHO, carbohydrates
[a] Children with end-stage liver disease awaiting liver transplantation
[b] Patients with hepatocellular carcinoma after curative resection (99 with cirrhosis)

The general conclusion was that physicians might not recommend the use of BCAAs in cirrhotic patients, in the presence of advanced disease, or with impending or overt encephalopathy. Based on this opinion, BCAAs are not provided by national health services in most European countries or in the United States.

Alternatively, physicians can make their own decisions based on personal experience or may postpone any decision until new studies clarify the reasons for the different results. Finally, the scientific community may accept evidence supporting the beneficial effects of BCAAs in selected patients on the basis of the results of the two largest studies in advanced lives disease patients. This cohort developed overt encephalopathy with increasing rates of alimentary proteins or had frankly altered mental states with dietary proteins at doses that maintain the nitrogen balance.

Nutrition

The nutritional effects of BCAAs are difficult to prove on a statistical basis. Few data are available, and advanced liver disease makes it difficult to measure the effects of therapy on nutrition. The best variable with which to study the nutritional effects of therapy is calculation of the nitrogen balance, which was performed in only eight studies.[16,18–22,24,25] In one study, control treatment did not include a comparable nitrogen supply.[19] In the remaining reports, no clear-cut differences were demonstrated between BCAAs and alimentary proteins or when several determinations were performed at different nitrogen intake levels.[18,24] Only two studies[21,25] reported favorable results with BCAAs, implying a potential effect of exogenous BCAAs on nitrogen metabolism, a result indirectly supported by laboratory studies. The difference in favor of BCAAs is thin, however, and more studies are needed to rule out the possible bias of liver disease on nutritional parameters.

Consensus statement

On the basis of this uncertain evidence, the European Society for Parenteral and Enteral Nutrition asked a consensus group to generate guidelines for nutrition

in those with liver disease or who are undergoing transplantation. The document, reported in 1997,[31] demonstrates how much our knowledge of nutritional problems in cirrhosis has improved but also how many areas still deserve attention. Several issues are probably settled, but new questions need answers.

First, patients with cirrhosis tend to be hypermetabolic and spend most of their time in a metabolic state similar to that seen with prolonged fasting.[32] Conflicting results reported in the literature are probably due to differences in the way results are expressed (per kilogram body weight, fat-free mass, or body cell mass).[33] The reason for accelerated catabolism may be the hormonal imbalance, which is secondary to defective glycogen stores; the consequence is higher-than-normal protein requirements to cope with increased gluconeogenesis.[34] There is evidence that 1.2–1.5 g of protein per kilogram body weight per day are needed to achieve nitrogen balance.

Second, also in the presence of advanced disease, most patients tolerate normal or even increased protein intake, without risk of hepatic encephalopathy. This statement contrasts with the usual practice of restricting proteins to prevent hepatic coma. In hypermetabolic patients, the benefit of a low-protein diet is minimum when compared to the large amount of amino acids entering the systemic circulation owing to protein degradation.[35] In contrast, malnourished patients may benefit from nutritional support with amino acids or oral proteins. Decreased morbidity and mortality are related to both improved nutrition and improved liver function.[30]

To prevent accelerated fasting and malnutrition, a modified eating pattern, based on several meals and a late evening snack, is useful.[36] Only in malnourished patients may amino acid supplements (or BCAA supplements in protein-intolerant patients) be considered to meet protein requirements and to break the vicious circle linking malnutrition, hypermetabolism, and net protein loss. Finally, in patients with mild chronic encephalopathy or preclinical (latent) alterations of psychomotor function, BCAA supplements may help provide the necessary nitrogen intake with no detrimental effect on mental state, perhaps even improving it. Adequate dietary proteins may be a prerequisite for the beneficial effects of BCAA supplements.

The last statement is based on studies with stable isotopes. BCAA-enriched, aromatic amino acid-free solutions, in combination with glucose and insulin, markedly decrease the rate of protein degradation.[37] When aromatic amino acids are given in combination with BCAAs, protein synthesis is increased,[38] further increasing net nitrogen sparing. There is evidence that several nonessential amino acids become nutritionally essential in patients with cirrhosis, and diets or supplements poor in or free of specific amino acids may fail to promote nitrogen sparing.[30,40] The prevailing fuel substrate may also be involved.[41]

Perspectives for the future

Encephalopathy and nutrition were the outcomes considered so far. It is time to consider more subjective, clinically sound endpoints and to conduct cost/benefit and cost/efficacy analyses. We need to know whether nutritional support prevents or delays complications in patients with uncomplicated cirrhosis and ultimately increases long-term survival. These outcomes have been tested in only a few studies. Daily supplements of 1000 kcal and 34 g protein for 1 year reduce hospital admission in patients with cirrhosis of alcoholic origin, with no effects on long-term survival.[42] Nutritional supplements providing 16 g BCAAs per day for 7–62 months delay mortality by 2 years for up to 4 years after inclusion into the study.[43] In patients undergoing curative resection of hepatocellular carcinoma, in most cases superimposed on cirrhosis, perioperative nutritional support with BCAAs reduces liver function loss and prevents complications.[44] Finally, 1-year oral administration of BCAAs after curative resection of hepatocellular carcinoma improves the clinical features and laboratory data without increasing tumor recurrence. This is mainly the case with more severely affected patients or patients undergoing major resections.[28] All these data, biased by some flaws,[44] need independent validation.

Liver transplantation is a new area of research. Preoperative malnutrition increases posttransplant morbidity and mortality in those with cirrhosis,[45] and adequate nutritional support is warranted.[46] It is also time to add new outcomes as primary endpoints. Subjective measures of health assessment, including the patient's overall well-being and reflecting mental and physical functioning, may replace biochemical data for measuring the results of long-term therapy.[47] Patients are more concerned about quality of life and disability than about longevity,[48] and a quantitative assessment of health-related quality of life may be considered in the evaluation of any therapeutic trial. This is mainly the case with chronic diseases, including cirrhosis, where long-term survival is not at risk and the goal of therapeutic interventions is to maintain patients symptom-free and living in the community. In an Italian survey,[49] muscle cramping, sometimes associated with malnutrition and electrolyte imbalance, was the symptom more closely associated to poor health-related quality of life in patients with complicated and uncomplicated cirrhosis. This new, unexplored area of quality of life in relation to nutritional intervention deserves attention.

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